Synthetic Organic Chemicals

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The Resolution of Racemic Substances

THE separation of optical isomers is a difficult task, and in spite of the interest in recent years, most of the methods in use at the present time are traceable to work done by Pasteur, with tartaric acid. In fact, if it had not happened that Pasteur's laboratory was relatively cool when he attempted the crystallization of sodium ammonium tartrate, very little might, even now, be known about optical isomers.

When a warm solution of sodium ammonium racemate is allowed to crystallize, only one compound separates. But if the temperature is lowered below the so-called transition point, two crystalline forms appear—each the mirror image of the other. These can be separated mechanically by careful handling and the two types when redissolved separately show optical rotation in opposite directions. However, on account of the limitations of the method, it is seldom used, although other racemic substances, including zinc ammonium lactate, iso-hydrobenzoin, camphoric acid, and asparagine, have been resolved by separating the two kinds of crystals.

A second method for obtaining the active forms from racemates also was discovered by Pasteur. He found that certain molds, yeasts, and bacteria sometimes destroy one isomer more rapidly than the other, and that if the proper conditions are maintained, only one finally remains. By choosing the right organism, either isomer may be selected for attack, but, unfortunately, half of the original racemate is destroyed in the process and the yields are small.

The most common means of separating two optically active components is by combining them with the active form of another substance. If, for example, a resolvable base is united with *d*-tartaric acid, two kinds of salt molecules will be formed. These may be described by referring to their optical activity as *d-d* and *l-d*. These salts are no longer exactly alike in their properties and may be separated by fractional crystallization. The more insoluble form, usually the *l-d*, is thus obtained in a pure state, and can be broken up by a suitable reagent to obtain the levo form of the original base.

Bases can nearly always be resolved by combining with optically active acids, as just described. Conversely, acids may be separated into optical enantiomorphs by uniting with alkaloids or active amines, such as menthylamine, bornylamine, and β-naphthol phenylaminomethane. The alpha-amino acids are too weakly acidic to form stable salts with alkaloids, but Emil Fischer found that this could be overcome by converting the acids to their formyl, benzoyl, or p-nitrobenzoyl derivatives. Amines are sometimes difficult to separate, although helicin, an optically active salicylaldehyde glucoside,

has been used successfully for some of them. Sugars, as well as other aldehydes and ketones, have been resolved by means of optically active hydrazines, such as menthylhydrazine and amylphenylhydrazine.

Alcohols are combined with optically active acids and the esters hydrolyzed later, after separation of the two forms. Another useful and ingenious method for alcohols, which was devised by Pickard and Kenyon, consists in first forming the half-ester with a dibasic acid. The remaining carboxyl group of the acid (phthalic or succinic) can be united with an active alkaloid. In general, it is customary, whenever possible, to introduce a carboxyl group into the product to be resolved since there are a relatively larger number of active bases with which the –COOH group can react.

Optically active compounds other than those mentioned may best be prepared by starting with an active substance and avoiding racemization in the subsequent reactions. One example in the aliphatic group is the formation of optically active nitro-compounds from the corresponding alcohols.

An interesting modification of direct resolution starts with an optically active molecule, followed by the introduction of a second asymmetric carbon atom. This procedure is termed asymmetric synthesis and may be illustrated by the formation of *l*-menthylacrylate and its subsequent bromination to yield *l*-menthyl *l*-dibromoacrylate and *l*-menthyl *d*-dibromoacrylate in equal amounts. These may be separated by fractional crystallization and then hydrolyzed to obtain both active isomers of dibromoacrylic acid.

As mentioned previously, the *d-l* enantiomorph is usually the more insoluble, and hence, the easier to isolate in the pure state. Further evaporation of the mother liquor allows the soluble isomer to crystallize, but it is always contaminated with the other. To isolate the second active form usually is more difficult. When possible, the best means is to use the other active form of the same resolving agent. Where the *l* base is isolated with *d*-tartaric acid, the *d* base usually combines with *l*-tartaric acid to form the less soluble salt.

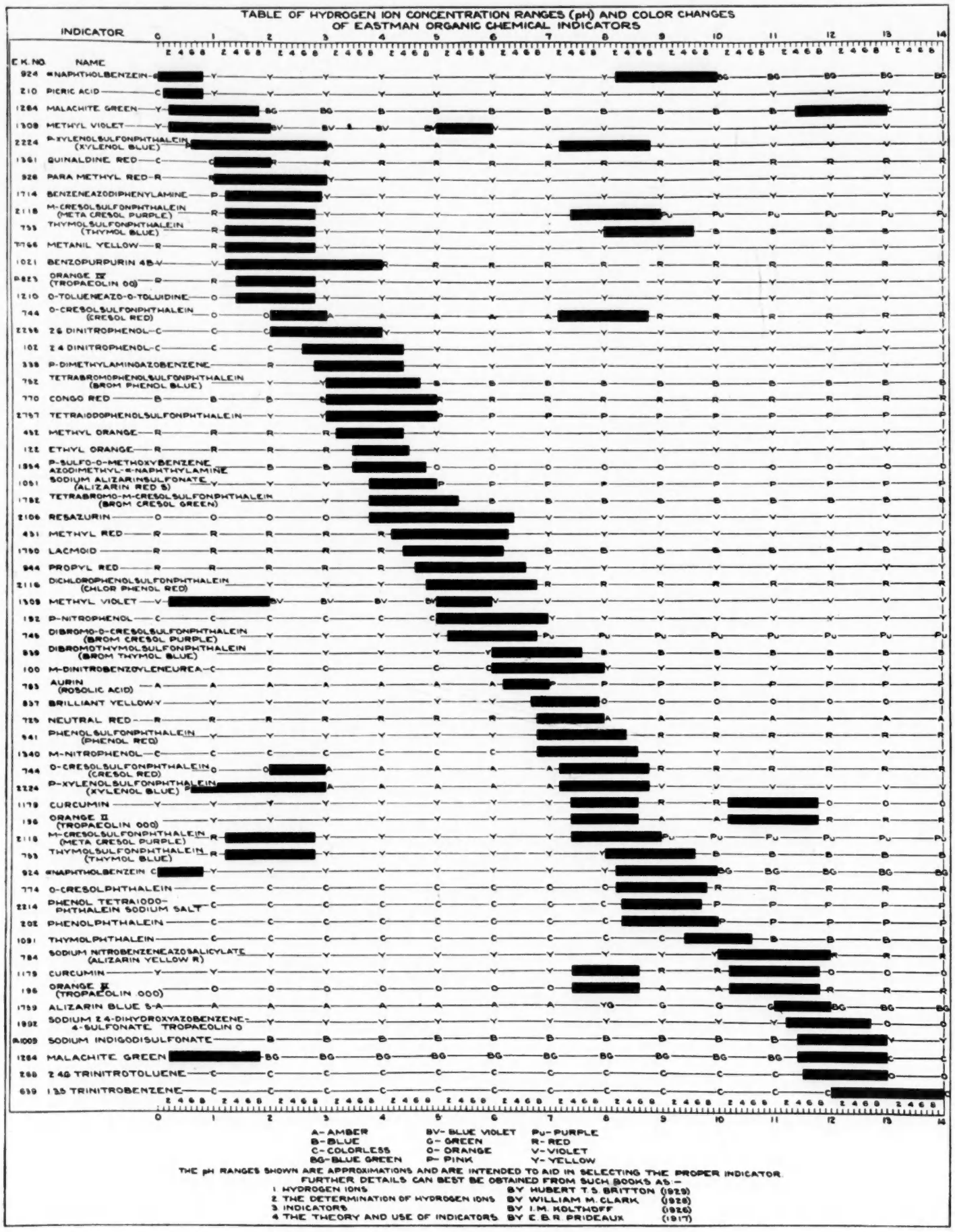
Another method uses, successively, two resolving agents to form insoluble salts with the different isomers. For instance, both brucine and strychnine are used to resolve racemic benzoylalanine. The brucine unites with *dl*-benzoylalanine to give a mixture of the two salts, of which the brucine *l*-benzoylalanine is the less soluble and can be isolated in a pure state. The remaining impure brucine *d*-salt is reconverted to the acid which is then combined with strychnine to give strychnine *d*-benzoylalanine, the more insoluble salt.

In still a different method, the residue from which one isomer has been separated is treated with the racemic instead of the active form of the resolving agent. In this case, all four possible isomers are formed, but the one of the *d-l* forms which will be present in largest amounts may be purified by recrystallization.

The actual resolution of optically active substances does not always run as smoothly as might be inferred in reading about them. In spite of the wide choice of resolving agents, it is often difficult to obtain a stable, crystalline compound which is necessary for fractional crystallization, and even when crystalline derivatives are obtained, the difference in solubility may be so small as to make separation impractical. The final removal of the resolving agent is also a troublesome operation. Salts may be broken up by treatment with alkali, but other compounds are not so easily reconverted. There is always a strong tendency for the active form to racemize during the process and thus undo the work so laboriously performed.

An Improved Indicator Chart

THE color changes shown below were obtained from actual laboratory observations on solutions buffered at definite pH values. The catalog numbers in the first column refer to our List No. 23. A 9" x 12" copy of this chart, printed on cardboard, will be sent to those who would find it useful.



THE pH RANGES SHOWN ARE APPROXIMATIONS AND ARE INTENDED TO AID IN SELECTING THE PROPER INDICATOR. FURTHER DETAILS CAN BEST BE OBTAINED FROM SUCH BOOKS AS:—

1. HYDROGEN IONS BY HUBERT T.S. BRITTON (1929)
2. THE DETERMINATION OF HYDROGEN IONS BY WILLIAM M. CLARK (1928)
3. INDICATORS BY I.M. KOLTHOFF (1926)
4. THE THEORY AND USE OF INDICATORS BY C.B.R. PRIDEAUX (1917)

Twenty-five New Eastman Organic Chemicals

Since the last issue of this bulletin twenty-five new chemicals have been prepared and added to our stock. Purity specifications and prices of these new products will be supplied on request.

Alanine Ethyl Ester Hydrochloride
Benzenepentacarboxylic Acid
Benzoylacetone
α-Bromoacetoacetanilide
p-Bromobenzoyl Chloride
d-Camphoroxime
Cinnamyl Chloride
Dibenzanthracene
2.4-Dinitrodiethylaniline
Diphenyl Triketone
β-Ethoxyethyl o-Benzoylbenzoate
Guaethol
p-Methylphenacyl Bromide
o-Nitrobenzaldehyde
p-Nitrophenyl iso-Cyanate
Pelargonamide
Pelargonyl Chloride
p-Phenylacetophenone
Phenyl n-Amyl Ketone
p-Phenylphenacyl Bromide
Phenyl Propionate
Resorcinol Diethyl Ether
Resorcinol Monoethyl Ether
Tri-p-cresyl Phosphite
p-Xylyl Alcohol

Eastman Organic Chemicals as Analytical Reagents

XXV Reagents for Bismuth.

CINCHONINE

Scott, STANDARD METHODS OF ANALYSIS I, 77 (1927)

The bismuth is first separated from other elements and precipitated as the basic carbonate. The carbonate is dissolved in a small amount of dilute nitric acid and made up to a definite volume with water. An aliquot part is then added to a solution of cinchonine and potassium iodide, producing a crimson or orange color which can be compared with that of a standard solution.

DIMETHYLGLYOXIME

Kubina and Plichta, Z. ANAL. CHEM. *72*, 11 (1927)

When hot solutions of bismuth chloride or nitrate are treated with one per cent dimethylglyoxime and concentrated ammonia, a bright yellow coloration is first formed, later resulting in a yellow precipitate. The reaction is very sensitive (1 part in 70,000), but the bulky precipitate is not suitable for quantitative work.

8-HYDROXYQUINOLINE

Berg, Z. ANAL. CHEM. *72*, 177 (1927)

Bismuth forms an insoluble orange-colored salt with 8-hydroxyquinoline under the proper conditions. To the bismuth solution in the form of nitrate is added tartaric acid and just enough ammonia or sodium hydroxide to neutralize. The solution is made faintly acid with acetic acid and after adding sodium acetate, the temperature is raised to 60° or 70° C. A cold acetone solution of 8-hydroxyquinoline is added and the mixture heated nearly to boiling. After filtering and washing, the precipitate can be accurately titrated bromimetrically.

PYROGALLOL

Feigl & Ordelt, Z. ANAL. CHEM. *65*, 448 (1925)

Bismuth is precipitated quantitatively by pyrogallol in very weakly acid solutions. The solution is first treated with ammonia to a slight turbidity which is then removed with a drop of dilute nitric acid. On adding a concentrated solution of pyrogallol and heating to boiling, a yellow crystalline precipitate is obtained. When filtered, washed, and dried at 110° C., it contains 62.84 per cent bismuth.